

AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning at page 49, line 19 and ending at page 50, line 13 with the following rewritten paragraph.

In some embodiments, the RNA, aptamer, peptide or protein reduces proliferation of the microorganisms by interacting with another molecule required for proliferation. In this case, many techniques in molecular biology can be employed to identify the cell proliferation molecule that interacts with the aptamer, peptide, or protein and the gene encoding this molecule. Conventional one and two hybrid systems, for example, can be readily adapted to identify molecules that bind to an aptamer, peptide, or protein described above, for example. Such approaches include:

- (1) the two-hybrid systems (Field & Song, *Nature* 340:245-246 (1989); Chien *et al.*, *Proc. Natl. Acad. Sci. USA* 88:9578-9582 (1991); and Young KH, *Biol. Reprod.* 58:302-311 (1998), all of which are expressly incorporated by reference in their entirety);
- (2) the reverse two-hybrid system (Leanna & Hannink, *Nucl. Acid Res.* 24:3341-3347 (1996), herein incorporated by reference in their entirety);
- (3) the repressed transactivator system (Sadowski *et al.*, U.S. Pat. No. 5,885,779), herein incorporated by reference in their entirety);
- (4) phage display systems (Lowman HB, *Annu. Rev. Biophys. Biomol. Struct.* 26:401-424 (1997), herein incorporated by reference in their entirety); and
- (5) GST/HIS pull down assays, mutant operators (Granger *et al.*, ~~WO 98/01879~~ WO 98/01579) and the like (See also Mathis G., *Clin. Chem.* 41:139-147 (1995); Lam K.S. *Anticancer Drug Res.*, 12:145-167 (1997); and Phizicky *et al.*, *Microbiol. Rev.* 59:94-123 (1995), all of which are expressly incorporated by reference in their entirety).

Please replace the paragraph beginning at page 52, line 25 and ending at page 53, line 14 with the following rewritten paragraph.

Appl. No. : 10/032,393
Filed : December 21, 2001

The number of nucleotide and protein sequences available in database systems has been growing exponentially for years. For example, the complete nucleotide sequences of *Caenorhabditis elegans* and several bacterial genomes, including *E. coli*, *Aeropyrum pernix*, *Aquifex aeolicus*, *Archaeoglobus fulgidus*, *Bacillus subtilis*, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Clostridium tetani*, *Corynebacterium diphtheria*, *Deinococcus radiodurans*, *Haemophilus influenzae*, *Helicobacter pylori* 26695, *Helicobacter pylori* J99, *Methanobacterium thermoautotrophicum*, *Methanococcus jannaschii*, *Mycobacterium tuberculosis*, *Mycoplasma genitalium*, *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, *Pyrococcus abyssi*, *Pyrococcus horikoshii*, *Rickettsia prowazekii*, *Synechocystis* PCC6803, *Thermotoga maritima*, *Treponema pallidum*, *Bordetella pertussis*, *Campylobacter jejuni*, *Clostridium acetobutylicum*, *Mycobacterium tuberculosis* CSU#93, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Pyrobaculum aerophilum*, *Pyrococcus furiosus*, *Rhodobacter capsulatus*, *Salmonella typhimurium*, *Streptococcus mutans*, *Streptococcus pyogenes*, *Ureaplasma urealyticum* and *Vibrio cholera* are available. This nucleotide sequence information is stored in a number of databanks, such as GenBank, the National Center for Biotechnology Information (NCBI), the Genome Sequencing Center (<http://genome.wustl.edu/gsc/salmonella.shtml>), and the Sanger Centre (http://www.sanger.ac.uk/projects/S_typhi) which are publicly available for searching. The Genome Sequencing Centre database can be accessed on the internet by entering the following quoted text, "genome.wustl.", in the address bar of a web browser, such as Internet Explorer or Netscape, followed immediately by "edu". The Sanger Centre database can be accessed on the internet by entering the following quoted text, "www.sanger.", in the address bar of a web browser, such as Internet Explorer or Netscape, followed immediately by "ac.uk".

Please replace the paragraph beginning at page 53, line 25 and ending at page 54, line 4 with the following rewritten paragraph.

BLAST, an acronym for "Basic Local Alignment Search Tool," is a family of programs for database similarity searching. The BLAST family of programs includes: BLASTN, a nucleotide sequence database searching program, BLASTX, a protein database searching program where the

Appl. No. : 10/032,393
Filed : December 21, 2001

input is a nucleic acid sequence; and BLASTP, a protein database searching program. BLAST programs embody a fast algorithm for sequence matching, rigorous statistical methods for judging the significance of matches, and various options for tailoring the program for special situations. ~~Assistance in using the program can be obtained by e-mail at blast@ncbi.nlm.nih.gov.~~ tBLASTX can be used to translate a nucleotide sequence in all three potential reading frames into an amino acid sequence.

Please replace the paragraph beginning at page 54, line 17 and ending at page 55, line 5 with the following rewritten paragraph.

In one embodiment of the present invention, an operon is identified and then dissected to determine which gene or genes are required for proliferation. Operons can be identified by a variety of means known to those in the art. For example, the RegulonDB DataBase described by Huerta et al. (*Nucl. Acids Res.* 26:55-59, 1998), which may also be found on the website http://www.cifn.unam.mx/Computational_Biology/regulondb/, the disclosures of which are incorporated herein by reference in their entirety, provides information about operons in *Escherichia coli*. The Subtilist database, which can be accessed on the internet by entering the following quoted text, "bioweb.pasteur.", in the address bar of a web browser, such as Internet Explorer or Netscape, followed immediately by "fr/GenoList/SubtiList", (<http://bioweb.pasteur.fr/GenoList/SubtiList>) (Moszer, I., Glaser, P. and Danchin, A. (1995) *Microbiology* 141: 261-268 and Moszer, I (1998) *FEBS Letters* 430: 28-36, the disclosures of which are incorporated herein in their entirety), may also be used to predict operons. This database lists genes from the fully sequenced, Gram-positive bacteria, *Bacillus subtilis*, together with predicted promoters and terminator sites. This information can be used in conjunction with the *Staphylococcus aureus* genomic sequence data to predict operons and thus produce a list of the genes affected by the antisense nucleic acids of the present invention. The TIGR microbial database, which can be accessed on the internet by entering the following quoted text, "www.tigr.", in the address bar of a web browser, such as Internet Explorer or Netscape, followed immediately by "org", has an incomplete version of the *Enterococcus faecalis* genome http://www.tigr.org/cgi-bin/BlastSearch/bblast.cgi?organism=e_faecalis. One can take a nucleotide sequence and BLAST it for homologs.

Appl. No. : 10/032,393
Filed : December 21, 2001

Please replace the paragraph beginning at page 119, line 26 and ending at page 120, line 3 with the following rewritten paragraph.

Operons are predicted by looking for all adjacent genes in a genomic region that lie in the same orientation with no large noncoding gaps in between. First, full length ORFs complementary to the antisense molecules are identified as described above. Adjacent ORFs are then identified and their relative orientation determined either by directly analyzing the genomic sequences surrounding the ORFs complementary to the antisense clones or by extracting adjacent ORFs from the collection obtained through whole genome ORF analysis described above followed by ORF alignment. Operons predicted in this way may be confirmed by comparison to the arrangement of the homologous genes in the *Bacillus subtilis* complete genome sequence, as reported by the genome database compiled at Institut Pasteur Subtilist Release R15.1 (June 24, 1999) which can be found at ~~http://bioweb.pasteur.fr/GenoList/SubtiList/~~ on the internet by entering the following quoted text, "bioweb.pasteur.", in the address bar of a web browser, such as Internet Explorer or Netscape, followed immediately by "fr/GenoList/SubtiList". The *Bacillus subtilis* genome is the only fully sequenced and annotated genome from a Gram-positive microorganism, and appears to have a high level of similarity to *Staphylococcus aureus* both at the level of conservation of gene sequence and genomic organization including operon structure. Annotation of some of the DNA sequences in some of the aforementioned databases is lacking, but comparisons may be made to *E. coli* using tools such as BLASTX. Public or proprietary databases may be used to analyzed *E. faecalis* sequences as well as the databases listed above.